

Patent claims

1. Combined use of a pulmonary surfactant and a PDE2 inhibitor for preventing or reducing the onset of symptoms of a disease, or treating or reducing the severity of a disease in a patient in need thereof, in which disease pulmonary surfactant malfunction and/or phosphodiesterase 2 (PDE2) activity is detrimental.
2. Use of a combination of a pulmonary surfactant and a PDE2 inhibitor for the preparation of a medicament for preventing or reducing the onset of symptoms of a disease, or treating or reducing the severity of a disease in a patient in need thereof, in which disease pulmonary surfactant malfunction and/or phosphodiesterase 2 (PDE2) activity is detrimental.
3. Method for preventing or reducing the onset of symptoms of a disease in which pulmonary surfactant malfunction and/or phosphodiesterase 2 (PDE2) activity is detrimental, or treating or reducing the severity of a disease in which pulmonary surfactant malfunction and/or phosphodiesterase 2 (PDE2) activity is detrimental by administering to a patient in need thereof an effective amount of (1) a pulmonary surfactant and (2) a PDE2 inhibitor.
4. The method according to claim 3, wherein an effective amount of (1) a pulmonary surfactant and (2) a PDE2 inhibitor is administered simultaneously to a patient in need thereof.
5. The method according to claim 3, wherein an effective amount of (1) a pulmonary surfactant and (2) a PDE2 inhibitor are administered in succession, close in time or remote in time, in any order whatever to a patient in need thereof.
6. Use or method according to any of claims 1 to 5, wherein the pulmonary surfactant is selected from the group consisting of PORACTANT ALFA, BERACTANT, BOVACTANT, COLFOSCERIL PALMITATE, SURFACTANT-TA, CALFACTANT, PUMACTANT, LUSUPULTIDE and SINAPULTIDE.
7. Use or method according to claim 6, wherein the pulmonary surfactant is LUSUPULTIDE.
8. Use or method according to any of claims 1 to 5, wherein the PDE2 inhibitor is selected from the group consisting of N-Benzyl-2-[5-fluoro-2-methyl-1(Z)-(3,4,5-trimethoxybenzylidene)inden-3-yl]acetamide, 2-(3'-Aminobiphenyl-4-ylmethyl)-9-(1-methyl-4-phenylbutyl)hypoxanthine, N-Benzyl-2-[5-fluoro-2-methyl-1(Z)-(3,4,5-trimethoxybenzylidene)inden-3-yl]acetamide, 2-(3'-Aminobiphenyl-4-ylmethyl)-9-(1-methyl-4-phenylbutyl)hypoxanthine, 2-Benzyl-9-(1-methyl-4-phenylbutyl)hypoxanthine, 2-(3,4-Dichlorobenzyl)-9-[1-(1-hydroxyethyl)-4-phenylbutyl]hypoxanthine, 2-(4-Fluorobenzyl)-9-(1-methyl-4-phenylbutyl)hypoxanthine, 9-(1-Methyl-4-phenylbutyl)-2-[4-(3-thienyl)benzyl]hypoxanthine, 1-[5-[9-[1-(1-Hydroxyethyl)-4-phenylbutyl]hypoxanthin-2-ylmethyl]-2-methoxyphenylsulfonyl]piperidine-4-

carboxylic acid, 2-(Biphenyl-4-yl)-9-(1-methyl-4-phenylbutyl)-6,9-dihydro-1H-purin-6-one, 2-(4-Chlorophenyl)-9-[1-(1-hydroxyethyl)heptyl]-6,9-dihydro-1H-purin-6-one, 2-Cyclohexyl-9-[1-(1-hydroxyethyl)-4-phenylbutyl]-6,9-dihydro-1H-purin-6-one, 2-Cyclopropyl-9-(1-methyl-4-phenylbutyl)-6,9-dihydro-1H-purin-6-one, 2-(1,3-Benzodioxol-5-yl)-9-(1-methyl-4-phenylbutyl)-6,9-dihydro-1H-purin-6-one, erythro-9-(2-hydroxy-3-nonyl)adenine, 9-(6-Phenyl-2-oxohex-3-yl)-2-(3,4-dimethoxybenzyl)-purin-6-one, 6-(3,4-Dimethoxy-benzyl)-1-[1-(1-hydroxy-ethyl)-4-phenyl-butyl]-3-methyl-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one, N-benzyl-2-(6-fluoro-2-methyl-3-pyridin-4-ylmethylene-3H-inden-1-yl)-acetamide, (1Z)-N-benzyl-2-[6-fluoro-2-methyl-3-(3,4,5-trimethoxybenzylidene)-3H-inden-1-yl]-acetamide, N-Benzyl-2-[5-fluoro-2-methyl-1-[(Z)-(pyridin-4-yl)methylene]-1H-inden-3-yl]acetamide hydrochloride, 4-[N-[4-[9-[N-Methyl-N-(3-phenylpropyl)amino]hypoxanthin-2-ylmethyl]phenyl]carbamoyl]piperidine-1-carboxylic acid benzyl ester, 4-[N-[4-[9-(N-hexyl-N-methylamino)hypoxanthin-2-ylmethyl]phenyl]carbamoyl]piperidine-1-carboxylic acid benzyl ester, 2-(3,4-Dimethoxybenzyl)-9-[N-methyl-N-(3-phenylpropyl)amino]hypoxanthine, 9-[N-Methyl-N-(3-phenylpropyl)amino]-2-[4-(4-methylpiperazin-1-ylsulfonyl)benzyl]hypoxanthine, 2-(3,4-Dimethoxybenzyl)-7-[1(R)-[1(R)-hydroxyethyl]-4-phenylbutyl]-5-methylimidazo[5,1-f][1,2,4]triazin-4(3H)-one, 7-(1-Acetylpentyl)-5-methyl-2-(4-methylbenzyl)imidazo[5,1-f][1,2,4]triazin-4(3H)-one, 7-(1-Acetylhexyl)-5-methyl-2-(4-methylbenzyl)imidazo[5,1-f][1,2,4]triazin-4(3H)-one, 2-(3,4-Dimethoxybenzyl)-7-[1-(1-hydroxyethyl)-5-hexenyl]-5-methylimidazo[5,1-f][1,2,4]triazin-4(3H)-one, and the pharmaceutically acceptable salts of these compounds.

9. Use or method according to any of claims 1 to 8, wherein the PDE2 inhibitor is selected from the group consisting of N-Benzyl-2-[5-fluoro-2-methyl-1(Z)-(3,4,5-trimethoxybenzylidene)inden-3-yl]acetamide, 2-(3'-Aminobiphenyl-4-ylmethyl)-9-(1-methyl-4-phenylbutyl)hypoxanthine, N-Benzyl-2-[5-fluoro-2-methyl-1(Z)-(3,4,5-trimethoxybenzylidene)inden-3-yl]acetamide, 2-(3'-Aminobiphenyl-4-ylmethyl)-9-(1-methyl-4-phenylbutyl)hypoxanthine, 2-Benzyl-9-(1-methyl-4-phenylbutyl)hypoxanthine, 2-(3,4-Dichlorobenzyl)-9-[1-(1-hydroxyethyl)-4-phenylbutyl]hypoxanthine, 2-(4-Fluorobenzyl)-9-(1-methyl-4-phenylbutyl)hypoxanthine, 9-(1-Methyl-4-phenylbutyl)-2-[4-(3-thienyl)benzyl]hypoxanthine, 1-[5-[9-[1-(1-Hydroxyethyl)-4-phenylbutyl]hypoxanthin-2-ylmethyl]-2-methoxyphenylsulfonyl]piperidine-4-carboxylic acid, 2-(Biphenyl-4-yl)-9-(1-methyl-4-phenylbutyl)-6,9-dihydro-1H-purin-6-one, 2-(4-Chlorophenyl)-9-[1-(1-hydroxyethyl)heptyl]-6,9-dihydro-1H-purin-6-one, 2-Cyclohexyl-9-[1-(1-hydroxyethyl)-4-phenylbutyl]-6,9-dihydro-1H-purin-6-one, 2-Cyclopropyl-9-(1-methyl-4-phenylbutyl)-6,9-dihydro-1H-purin-6-one, 2-(1,3-Benzodioxol-5-yl)-9-(1-methyl-4-phenylbutyl)-6,9-dihydro-1H-purin-6-one, erythro-9-(2-hydroxy-3-nonyl)adenine, 9-(6-Phenyl-2-oxohex-3-yl)-2-(3,4-dimethoxybenzyl)-purin-6-one, 6-(3,4-Dimethoxy-benzyl)-1-[1-(1-hydroxy-ethyl)-4-phenyl-butyl]-3-methyl-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one, N-benzyl-2-(6-fluoro-2-methyl-3-pyridin-4-ylmethylene-3H-inden-1-yl)-acetamide, (1Z)-N-benzyl-2-[6-fluoro-2-methyl-3-(3,4,5-trimethoxybenzylidene)-3H-inden-1-yl]-acetamide, N-Benzyl-2-[5-fluoro-2-methyl-1-[(Z)-(pyridin-4-yl)methylene]-1H-inden-3-yl]acetamide hydrochloride, 4-[N-[4-[9-[N-Methyl-N-(3-phenylpropyl)amino]hypoxanthin-2-ylmethyl]phenyl]carbamoyl]piperidine-1-carboxylic acid benzyl ester, 4-[N-[4-[9-(N-hexyl-N-

methylamino)hypoxanthin-2-ylmethyl]phenyl]carbamoyl]piperidine-1-carboxylic acid benzyl ester, 2-(3,4-Dimethoxybenzyl)-9-[N-methyl-N-(3-phenylpropyl)amino]hypoxanthine, 9-[N-Methyl-N-(3-phenylpropyl)amino]-2-[4-(4-methylpiperazin-1-ylsulfonyl)benzyl]hypoxanthine, 2-(3,4-Dimethoxybenzyl)-7-[1(R)-[1(R)-hydroxyethyl]-4-phenylbutyl]-5-methylimidazo[5,1-f][1,2,4]triazin-4(3H)-one, 7-(1-Acetylpentyl)-5-methyl-2-(4-methylbenzyl)imidazo[5,1-f][1,2,4]triazin-4(3H)-one, 7-(1-Acetylhexyl)-5-methyl-2-(4-methylbenzyl)imidazo[5,1-f][1,2,4]triazin-4(3H)-one, 2-(3,4-Dimethoxybenzyl)-7-[1-(1-hydroxyethyl)-5-hexenyl]-5-methylimidazo[5,1-f][1,2,4]triazin-4(3H)-one, and the pharmaceutically acceptable salts of these compounds.

10. Use or method according to any of claims 1 to 7, wherein the disease in which pulmonary surfactant malfunction and/or phosphodiesterase 2 (PDE2) activity is detrimental is ARDS or Asthma bronchiale.

11. Use or method according to any of claims 1 to 9, wherein the disease in which pulmonary surfactant malfunction and/or phosphodiesterase 2 (PDE2) activity is detrimental is selected from the group consisting of ALI, IRDS, ARDS and Asthma bronchiale.

12. Pharmaceutical composition suited for the use or method according to claims 1 to 8 comprising an effective amount of a pulmonary surfactant and an effective amount of a PDE2 inhibitor.

13. Pharmaceutical composition according to claim 12, comprising as a fixed combination

- an effective amount of a pulmonary surfactant and
- an effective amount of a PDE2 inhibitor, and optionally
- a pharmaceutically acceptable carrier.

14. Pharmaceutical composition according to claim 13, which is a fixed pharmaceutical composition for intratracheally or intrabronchially instillation.

15. Pharmaceutical composition according to claim 12, comprising as a free combination

- an effective amount of a pulmonary surfactant and optionally a pharmaceutically acceptable carrier and
- an effective amount of a PDE2 inhibitor and optionally a pharmaceutically acceptable carrier.

16. Pharmaceutical composition according to any of claims 12 to 15, wherein the pulmonary surfactant is selected from the group consisting of PORACTANT ALFA, BERACTANT, BOVACTANT, COLFOSCERIL PALMITATE, SURFACTANT-TA, CALFACTANT, PUMACTANT, LUSUPULTIDE OR SINAPULTIDE.

17. Pharmaceutical composition according to any of claims 12 to 16, wherein the pulmonary surfactant is LUSUPULTIDE.

18. Pharmaceutical composition according to any of claims 12 to 15, wherein the PDE2 inhibitor is selected from the group consisting of N-Benzyl-2-[5-fluoro-2-methyl-1(Z)-(3,4,5-trimethoxybenzylidene)inden-3-yl]acetamide, 2-(3'-Aminobiphenyl-4-ylmethyl)-9-(1-methyl-4-phenylbutyl)hypoxanthine, N-Benzyl-2-[5-fluoro-2-methyl-1(Z)-(3,4,5-trimethoxybenzylidene)inden-3-yl]acetamide, 2-(3'-Aminobiphenyl-4-ylmethyl)-9-(1-methyl-4-phenylbutyl)hypoxanthine, 2-Benzyl-9-(1-methyl-4-phenylbutyl)hypoxanthine, 2-(3,4-Dichlorobenzyl)-9-[1-(1-hydroxyethyl)-4-phenylbutyl]hypoxanthine, 2-(4-Fluorobenzyl)-9-(1-methyl-4-phenylbutyl)hypoxanthine, 9-(1-Methyl-4-phenylbutyl)-2-[4-(3-thienyl)benzyl]hypoxanthine, 1-[5-[9-[1-(1-Hydroxyethyl)-4-phenylbutyl]hypoxanthin-2-ylmethyl]-2-methoxyphenylsulfonyl]piperidine-4-carboxylic acid, 2-(Biphenyl-4-yl)-9-(1-methyl-4-phenylbutyl)-6,9-dihydro-1H-purin-6-one, 2-(4-Chlorophenyl)-9-[1-(1-hydroxyethyl)heptyl]-6,9-dihydro-1H-purin-6-one, 2-Cyclohexyl-9-[1-(1-hydroxyethyl)-4-phenylbutyl]-6,9-dihydro-1H-purin-6-one, 2-Cyclopropyl-9-(1-methyl-4-phenylbutyl)-6,9-dihydro-1H-purin-6-one, 2-(1,3-Benzodioxol-5-yl)-9-(1-methyl-4-phenylbutyl)-6,9-dihydro-1H-purin-6-one, erythro-9-(2-hydroxy-3-nonyl)adenine, 9-(6-Phenyl-2-oxohex-3-yl)-2-(3,4-dimethoxybenzyl)-purin-6-one, 6-(3,4-Dimethoxybenzyl)-1-[1-(1-hydroxy-ethyl)-4-phenyl-butyl]-3-methyl-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one, N-benzyl-2-(6-fluoro-2-methyl-3-pyridin-4-ylmethylene-3H-inden-1-yl)-acetamide, (1Z)-N-benzyl-2-[6-fluoro-2-methyl-3-(3,4,5-trimethoxybenzylidene)-3H-inden-1-yl]-acetamide, N-Benzyl-2-[5-fluoro-2-methyl-1-(Z)-(pyridin-4-yl)methylene]-1H-inden-3-yl]acetamide hydrochloride, 4-[N-[4-[9-[N-Methyl-N-(3-phenylpropyl)amino]hypoxanthin-2-ylmethyl]phenyl]carbamoyl]piperidine-1-carboxylic acid benzyl ester, 4-[N-[4-[9-(N-hexyl-N-methylamino)hypoxanthin-2-ylmethyl]phenyl]carbamoyl]piperidine-1-carboxylic acid benzyl ester, 2-(3,4-Dimethoxybenzyl)-9-[N-methyl-N-(3-phenylpropyl)amino]hypoxanthine, 9-[N-Methyl-N-(3-phenylpropyl)amino]-2-[4-(4-methylpiperazin-1-ylsulfonyl)benzyl]hypoxanthine, 2-(3,4-Dimethoxybenzyl)-7-[1(R)-[1(R)-hydroxyethyl]-4-phenylbutyl]-5-methylimidazo[5,1-f][1,2,4]triazin-4(3H)-one, 7-(1-Acetylhexyl)-5-methyl-2-(4-methylbenzyl)imidazo[5,1-f][1,2,4]triazin-4(3H)-one, 7-(1-Acetyloctyl)-5-methyl-2-(4-methylbenzyl)imidazo[5,1-f][1,2,4]triazin-4(3H)-one, 2-(3,4-Dimethoxybenzyl)-7-[1-(1-hydroxyethyl)-5-hexenyl]-5-methylimidazo[5,1-f][1,2,4]triazin-4(3H)-one, and the pharmaceutically acceptable salts of these compounds.

19. Pharmaceutical composition according to any of claims 12 to 18, wherein the PDE2 inhibitor is selected from the group consisting of N-Benzyl-2-[5-fluoro-2-methyl-1(Z)-(3,4,5-trimethoxybenzylidene)inden-3-yl]acetamide, 2-(3'-Aminobiphenyl-4-ylmethyl)-9-(1-methyl-4-phenylbutyl)hypoxanthine, N-Benzyl-2-[5-fluoro-2-methyl-1(Z)-(3,4,5-trimethoxybenzylidene)inden-3-yl]acetamide, 2-(3'-Aminobiphenyl-4-ylmethyl)-9-(1-methyl-4-phenylbutyl)hypoxanthine, 2-Benzyl-9-(1-methyl-4-phenylbutyl)hypoxanthine, 2-(3,4-Dichlorobenzyl)-9-[1-(1-hydroxyethyl)-4-phenylbutyl]hypoxanthine, 2-(4-Fluorobenzyl)-9-(1-methyl-4-phenylbutyl)hypoxanthine, 9-(1-Methyl-4-

phenylbutyl)-2-[4-(3-thienyl)benzyl]hypoxanthine, 1-[5-[9-[1-(1-Hydroxyethyl)-4-phenylbutyl]hypoxanthin-2-ylmethyl]-2-methoxyphenylsulfonyl]piperidine-4-carboxylic acid, 2-(Biphenyl-4-yl)-9-(1-methyl-4-phenylbutyl)-6,9-dihydro-1H-purin-6-one, 2-(4-Chlorophenyl)-9-[1-(1-hydroxyethyl)heptyl]-6,9-dihydro-1H-purin-6-one, 2-Cyclohexyl-9-[1-(1-hydroxyethyl)-4-phenylbutyl]-6,9-dihydro-1H-purin-6-one, 2-Cyclopropyl-9-(1-methyl-4-phenylbutyl)-6,9-dihydro-1H-purin-6-one, 2-(1,3-Benzodioxol-5-yl)-9-(1-methyl-4-phenylbutyl)-6,9-dihydro-1H-purin-6-one, erythro-9-(2-hydroxy-3-nonyl)adenine, 9-(6-Phenyl-2-oxohex-3-yl)-2-(3,4-dimethoxybenzyl)-purin-6-one, 6-(3,4-Dimethoxybenzyl)-1-[1-(1-hydroxy-ethyl)-4-phenyl-butyl]-3-methyl-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one, N-benzyl-2-(6-fluoro-2-methyl-3-pyridin-4-ylmethylene-3H-inden-1-yl)-acetamide, (1Z)-N-benzyl-2-[6-fluoro-2-methyl-3-(3,4,5-trimethoxybenzylidene)-3H-inden-1-yl]-acetamide, N-Benzyl-2-[5-fluoro-2-methyl-1-[(Z)-(pyridin-4-yl)methylene]-1H-inden-3-yl]acetamide hydrochloride, 4-[N-[4-[9-[N-Methyl-N-(3-phenylpropyl)amino]hypoxanthin-2-ylmethyl]phenyl]carbamoyl]piperidine-1-carboxylic acid benzyl ester, 4-[N-[4-[9-(N-hexyl-N-methylamino)hypoxanthin-2-ylmethyl]phenyl]carbamoyl]piperidine-1-carboxylic acid benzyl ester, 2-(3,4-Dimethoxybenzyl)-9-[N-methyl-N-(3-phenylpropyl)amino]hypoxanthine, 9-[N-Methyl-N-(3-phenylpropyl)amino]-2-[4-(4-methylpiperazin-1-ylsulfonyl)benzyl]hypoxanthine, 2-(3,4-Dimethoxybenzyl)-7-[1(R)-[1(R)-hydroxyethyl]-4-phenylbutyl]-5-methylimidazo[5,1-f][1,2,4]triazin-4(3H)-one, 7-(1-Acetylpentyl)-5-methyl-2-(4-methylbenzyl)imidazo[5,1-f][1,2,4]triazin-4(3H)-one, 7-(1-Acetylhexyl)-5-methyl-2-(4-methylbenzyl)imidazo[5,1-f][1,2,4]triazin-4(3H)-one, 2-(3,4-Dimethoxybenzyl)-7-[1-(1-hydroxyethyl)-5-hexenyl]-5-methylimidazo[5,1-f][1,2,4]triazin-4(3H)-one, and the pharmaceutically acceptable salts of these compounds.

20. Use of a pharmaceutical composition according to one of claims 12 to 19 for the treatment of a disease selected from the group consisting of ALI, IRDS, ARDS and Asthma bronchiale.

21. Method for preparing a pharmaceutical composition of the claims 12 to 14 comprising the step: mixing an effective amount of a pulmonary surfactant and a PDE2 inhibitor with a pharmaceutically acceptable carrier.